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Human epidermal growth factor receptor (EGFR, HER1) and HER2 are transmembrane receptors possessing intrinsic tyrosine kinase activity. Preclinical and more recently, clinical demonstration of synergism between antibodies directed at these receptors and chemotherapeutic agents has focused our present efforts on the characterization of synergistic interactions between cytotoxic drugs and inhibitors of the tyrosine kinase growth factor signalling cascade. While we have encountered obstacles, both clinical toxicity as well as operational difficulties, in the investigation of the chimeric monoclonal antibody C225 (directed at EGFR) + paclitaxel, as summarized within this report, we have subsequently proceeded rapidly and successfully with clinical evaluation of weekly trastuzumab (HER2-directed) + weekly paclitaxel. The present report describes our most recent efforts to molecularly characterize this synergy, to perform preclinical evaluation of antitubulin agents (taxanes, vincas, and epothilones) alone and in combination with farnesyl protein transferase inhibitors in mammary carcinoma cells, and to better define molecular predictors of response to inhibitors of mitogenic signal transduction, taxanes, and combinations of these agents.

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Andrew Lerch 2/2/99

PI - Signature Date

Department of Defense Breast Cancer Research Program

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Revised Statement of Work and Budget

May 1, 1998

New Project Title:

"Characterization of Synergistic Interactions Between Cytotoxic Agents and Inhibitors of the Tyrosine Kinase Growth Factor Receptor Signalling Cascade"

STATEMENT OF WORK

Task 1. Characterization and investigation of the synergy between cytotoxic drugs and inhibitors of the *tyrosine kinase* growth factor receptor signalling cascade (N. Rosen).

1. Define cell cycle and apoptotic effects of anti-EGFR, anti-HER2 receptor antibodies and farnesyl transferase inhibitors (FTIs) in MCF 10A cells and in MCF 10A cells transformed with H-ras, K-ras, or HER-2
2. In breast cancer systems, Taxol and FTI synergize in inducing mitotic phase block. We will now define whether upstream growth factor receptor blockade with anti-EGFR or anti-HER2 has similar synergy with FTI. If so, the phenomenology of the M-block and the pathway involved will be investigated and the possibility that triple therapy with FTI, antibody, and Taxol will be more effective will be investigated.
3. Our preliminary data suggests that the type of cellular response to inhibition of receptor tyrosine kinases is a function of whether or not they contain wild type or altered Rb or cyclin D. These data suggest that the clinical response to these antibodies alone or in combination with Taxol or FTI may also be dependent on the status of these gene products. We have engineered breast cancer cells containing high levels of EGFR or HER2 to overexpress cyclin D or E7, a protein that inactivates Rb. We will assess the response of these cells to antibody alone or in combinations with FTI or Taxol. The data will be compared to the clinical data correlating these abnormalities with response to therapy obtained in Task 3.3 (see below)

Task 2. Prelinical evaluation of epothilones, alone and in combination with *farnesyl protein transferase* inhibitors in mammary carcinoma models (S. Danishefsky)

1. Define differential effects between epothilones and taxanes on mammary carcinoma cells (e.g. microtubular polymerization, cell cycle regulatory effects, apoptosis)
2. Determine the effect of the combination of epothilone plus farnesyl protein transferase inhibitor in both EGFR-overexpressing and non-overexpressing cell lines.

Task 3. Determination of clinical response to inhibitors of mitogenic signal transduction, taxanes, and combinations of these agents
(P. Rosen, A. Seidman)

1. Expansion of existing 250 patient demographic computer database with additional data from patients receiving single agent taxane (from 9 MSKCC clinical trials 1991-1998, and non-protocol patients)
2. Creation of database for patients receiving single-agent paclitaxel plus Herceptin™ (rhuMab HER2) on MSKCC IRB protocol 98-28, and ultimately off-protocol, when Herceptin™ becomes commercially available (Fall 1998)
3. Characterization of molecular immunophenotype of pretreatment breast cancer tissue for association with clinical response to treatment with a) single agent taxane, b) taxane + Herceptin™:

    - HER-2/*neu*, heregulin, EGFR
    - p53
    - Rb
    - Cyclin D_1, E
    - $p27^{kip}$
    - Bcl-2, bax

4. Uni- and multi-variate statistical analysis of immunophenotypic features and patient demographic factors (e.g. age, extent of disease, extent of prior therapy, visceral dominant disease/not, performance status, prior anthracycline exposure)

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INTRODUCTION

Human epidermal growth factor receptor-1 (HER-1, EGFR) and -2 (HER-2/neu) are transmembrane receptors possessing intrinsic tyrosine kinase activity that bind a variety of ligands including EGF, transforming growth factor-α, and amphiregulin (1). Ligand binding induces activation of the tyrosine kinase leading to growth stimulation, but also perhaps to inhibition of apoptosis and other proliferative phenomena. The bioactivity of monoclonal antibodies (Mabs) against EGFR that we have produced is well documented (2). The human:murine chimeric version of Mab 225 (HC Mab 225) has been produced by ImClone Systems. We previously endeavored to evaluate the combination of this antibody with the cytotoxic chemotherapeutic agent paclitaxel, based on our observation of preclinical synergism for this combination against mammary carcinoma (3). Our statement of work has since been revised (see pages 4-7 within) due to operational difficulties encountered in the context of this government/private industry sponsored project. As a natural outgrowth of this work, and the recent demonstration of meaningful clinical synergy between the recombinant humanized monoclonal antibody directed at HER-2/neu (trastuzumab, Herceptin™, Genentech, Inc.)(4), we now have refocused our efforts. Two assumptions have directed our studies. We postulate that the effects of the antireceptor antibodies are due to interruption of the signalling cascade that is initiated by receptor activation. While this is generally assumed, it has not been rigorously proven. Second, although Herceptin has clinical activity, it is relatively modest, occurring only in a minority of patients whose tumors overexpress the HER2 protein. We presume that this is because the antibody is a relatively ineffective inhibitor of receptor function ands that a more effective inhibitor would have greater clinical efficacy. This is an unproven speculation. An alternative possibility is that the HER2 protein is required for breast cancer cell growth only in a minority of patients with overexpression. We here report on our recent and ongoing laboratory and correlative science research to refine our understanding of these phenomena and to develop improved therapies based on these findings in work directed at several tasks:

1. Characterization of the synergistic interactions between cytotoxic chemotherapeutic agents and inhibitors of the tyrosine kinase growth factor receptor signalling cascade
2. Preclinical evaluation of antitubulin agents (taxanes, vincas, epothilones), alone and in combination with farnesyl protein transferase inhibitors in mammary carcinoma cells
3. Definition of molecular predictors of clinical response to inhibitors of mitogenic signal transduction, taxanes, and combinations of these agents.

BODY

1. ORIGINAL WORK (through March 31, 1997):

The selection of patients for the clinical trials required that an efficient mechanism be established for the identification of potential candidates based on tumoral immunohistochemical expression of EGFR. All members of the Breast Cancer Medicine Service were involved in the procurement of paraffin-embedded tumor tissue, which was directed under the supervision of a designated research assistant to the laboratory of Dr. Peter Paul Rosen, in our Department of Pathology. Immunohistochemistry results were compiled in a computer database, and reports generated weekly for review by the Principal Investigator, in order to allow for timely identification of possible protocol candidates. To date, 12.1% of all breast carcinoma specimens have stained positively for EGFR.

The construction of a feasible phase I/II trial required the determination of the safety and pharmacokinetics of multiple administrations of the drug HC Mab 225. We therefore first performed an open-label dose-escalation study of four weekly infusions at the dose levels of 5 (n=1), 20 (n=2), 50 (n=1), and 100 mg/m2 (n=3) per week in patients with histologically documented advanced tumors over-expressing EGFR by immunohistochemistry (12 patients were enrolled at MSKCC, with 5 patients accrued at other centers). The median age was 60 years, and several tumor types were represented, including breast cancer. Only one patient experienced grade 3 toxicity, an episode of "aseptic meningitis" perhaps unrelated to drug administration; one grade 2 allergic reaction was noted. All other toxicities were grade 1, and included: acneiform rash (3 episodes), fatigue (2), hot flashes (1), anorexia (1), chills (1), flu-like symptoms (1), thrombocytopenia (1), stomatitis (1), elevation of alkaline phosphatase (1), and creatinine (1).

HC Mab 225 pharmacokinetics was assessed by the BIAcore (suface plasmon resonance) assay on serum samples drawn at 1/24, 3/24, 6/24, 1,2,5,8,15,22,26,and 28 days post-infusion. We sought to obtain a serum level of at least 20 nM, as preclinical evidence suggested that this would result in occupancy of a high proportion of receptors in target tissues (the notion of "saturation of receptors" does not apply since EGFR is widely distributed in normal organs). At the 50 mg/m2 dose level, the mean concentration of drug was greater than 20 nM for > 1 day. At 100 mg/m2 the mean concentration of drug was greater than 20 nM for >7 days, allowing for drug accumulation. Saturation of clearance was not seen. Hence we became confident that a trial employing weekly administrations of 100 mg/m2 doses of drug would be adequate to elicit the desired biological effects.

Our phase I/II trial of the combination of HC Mab 225 and paclitaxel was open to patients with histologically documented metastatic breast cancer, regardless of immunophenotypic expression of EGFR, with bidimensionally measurable disease, normal hematologic and organ

function, adequate performance status, no prior taxane, and < 2 prior chemotherapy regimens for metastatic disease. The study was designed to accrue 3 patients each at the following initial and subsequent doses in mg/m2 of HC Mab 225: 50/50, 100/100, 200/100, 400/100, with subsequent doses to be specified on the basis of the pharmacokinetic analysis. Paclitaxel was to be given at the conventional dose of 175 mg/m2 as a 3 hour infusion each 3 weeks, with standard premedications.

We initially treated 9 patients with the combination of weekly HC Mab 225 with "standard" paclitaxel dosing at 175 mg/m^2 via 3-hour infusion every 3 weeks. During this time, we observed a significant occurrence of moderate to severe skin toxicity: an erythematous follicular eruption of the face, trunk, and upper extremities of grade 2-3 severity in 4/9 evaluable patients. Skin biopsies of these lesions in 3 cases has demonstrated superficial folliculitis, with adjacent edema and mixed neutrophil and eosinophil, or pure neutrophil-rich inflammatory cell infiltrate with scattered histiocytes. Immunohistochemistry for EGFR in these skin biopsies revealed normal EGFR expression within keratinocytes. Of these 9 patients who were evaluable for antitumor response, two have shown minor tumor regression, but one of these had to discontinue treatment because of dermatologic toxicity.

These data suggest synergistic biologic activity between HC Mab 225 and paclitaxel, but in the skin. We were not able to assess if this synergy extends to the tumor, because the toxicity observed precluded adequate evaluation, both in terms of number of patients accrued and duration of follow-up. However, no early indications of synergistic anticancer benefit had been observed. While several patients consented to undergo skin biopsies in an effort to better elucidate the nature of the dermatologic reactions encountered, unfortunately no patient to date has consented to allow the perfomance of serial biopsies of accessible tumor tissue. Thus, we have, to date, been unable to perform the planned studies of EGFR and TGF-alpha regulation, EGFR phosphorylation, and apoptosis outlined in our original statement of work.

After careful examination of potential strategies to maximize synergistic antitumor effects, while minimizing potential for cutaneuos phenomonena, we chose to modify the administration schedule for these two agents. Given that paclitaxel may contribute to the toxicity (similarly frequent and severe cutaneous reactions with HC Mab 225 in combination with other cytotoxic agents, e.g. doxorubicin and cisplatin, have *not* been noted in other clinical trials in other solid tumors), we reassessed the Mab given weekly with an alternate schedule of paclitaxel -- paclitaxel was administered weekly at 80 mg/m^2 as a 1-hr infusion to the next three patients (with weekly HC Mab 225). In patients with ovarian carcinoma we have determined that this dose and schedule of paclitaxel is safe and effective (5). We have also completed a phase II and pharmacologic study of paclitaxel at 100 mg/m^2 in patients with minimally pretreated metastatic breast cancer, with a final response rate of 53.3% (95% C.I. 40-66%), including 3 complete remissions (6). Hence, we combined HC Mab 225 with an active regimen of paclitaxel, but with one that achieves lower peak plasma levels because of the lower total dose per administration, and additionally has been reported to cause less alopecia (follicle effect). The potential differences in paclitaxel's pharmacology (as a 175 mg/m^2/week 3-hour infusion every 3 weeks vs. as an 80 mg/m^2 infusion once weekly), and paclitaxel scheduling change on hair follicles motivated us to study this

alternative drug delivery plan. Indeed, if an important intratumoral synergistic effect is expected, one might expect this to be enhanced by weekly co-administration of both agents.

Clinical Protocol Update: Since October 1997 we have treated 3 patients with weekly coadministration of paclitaxel and HC Mab 225. All three patients experienced folliculitis: the first patient's was of grade 1 severity (protocol treatment was discontinued after 6 weeks due to disease progression), the second was of grade 3 severity and required discontinuation of protocol therapy despite a minor response after 6 weeks, and the third patient has experienced a grade 2 follicular skin reaction, presently stable at week 5 after early initiation of topical corticosteroid and systemic antibiotic (oral erythromycin) treatment. All three patients have been evaluated by a dermatologist, and skin reactions photographed.

As it seems the synergistic dermatologic phenomena encountered with paclitaxel + C225 MoAb combination therapy represents a significant obstacle to further clinical evaluation, we have shifted our focus to explore the potential for further exploiting the synergy of weekly paclitaxel (6) plus Herceptin™. We have entered 44 patients to our ongoing phase II trial of this regimen, and have observed quite promising preliminary results (Appendix A: abstract submitted to ASCO, 1999). Indeed, this regimen will be evaluated in a large, prospective randomized trial for metastatic breast cancer (CALGB 9840).

2. NEW WORK (September 15, 1997-September 14, 1998, as per revised statement of work, pages 5-7):

Task 1: Characterization and investigation of the synergy between cytotoxic drugs and inhibitors of the tyrosine kinase growth factor receptor signalling cascade (N. Rosen)

and

Task 2: Preclinical evaluation of antitubulin agents (taxanes, vincas, epothilones), alone and in combination with farnesyl protein transferase inhibitors in mammary carcinoma models (S. Danishefsky, N. Rosen):

Farnesyl transferase inhibitor (FTI) - paclitaxel Synergy:

Ras is an important element of signalling pathways that lies downstream of the HER kinases in the mitogenic cascade. FTIs were developed as inhibitors of the post-translational farnesylation of Ras. This modification is required for the localization of Ras to the plasma membrane and for Ras protein to transduce the growth signal. Mutational or upstream activation of Ras occurs in many tumors. The Ras gene is rarely, if ever, mutated in breast cancer, but Ras activation is presumed to be necessary for HER2, EGFR and other tyrosine kinases to exert their effects.

We have demonstrated that FTIs inhibit the growth of many breast cancer cell lines. We have shown that FTIs have multiple mechanisms of action. Their dominant effects on tumors are a function of the oncogenic mutations in that tumor. In some tumors, the FTI target is undoubtedly Ras, especially those in which H-Ras is mutated. In others, including several breast

models like MCF7, we have shown that the target is very unlikely to be Ras. Multiple other proteins are farnesylated - which of these are important for FTI induced growth inhibition is unclear.

In breast cancers with wild type p53, we showed that FTI induces the p53-dependent expression of p21 and causes G_1 arrest. If p53 or p21 function is abolished, G_1 arrest does not occur. However, such tumor cells die instead by undergoing unscheduled DNA synthesis in M phase and then programmed cell death. These data suggest that FTI may be useful in treating breast cancers with wild type p53 and Ras and that p53 status will in part control the type of response of the tumor to the drug.

We and others found that FTIs are relatively non-toxic in animals. These findings spurred us to evaluate whether FTI could be given together with cytotoxic agents. In breast cancer cell lines, we found that the effects of FTI were additive with doxorubicin, cisplatin and other chemotherapeutic agents. These data suggested that these combinations might be useful clinically. In addition, we found that FTI and paclitaxel were synergistic in their ability to block breast cancer cell growth. FTI sensitized the cell to the mitotic block induced by paclitaxel. This effect is only seen with agents that stabilize microtubules (taxanes, epothilones) and not with agents that prevent microtubule formation (vinca alkaloids). As FTI alone does not affect mitotic progression, this represents another potentially exploitable mechanism of FTI action.

These data have been used to plan clinical trials of FTI alone and in combination with other agents. Phase I trials have been completed with compounds made by Jannsen, Schering-Plough, and Merck. Single agent Phase II and Phase I/II trials of the FTI/paclitaxel combination are now in progress - these trials are in large part based on our data.

EGFR-FTI Synergy:

We have also shown that FTI synergizes with anti-EGFR antibodies to cause G_1 arrest in breast cancer model systems with mutated Ras. Since this genetic defect is uncommon in naturally occurring human breast cancer, it is not clear how clinically applicable this finding is. It is possible that FTI will work in concert or at least additively with modalities that perturb HER2 or EGFR signalling.

Our recent data shows that EGFR and HER2 work through Ras-dependent and independent (PI3 kinase and Stat) dependent pathways. FTI and antireceptor antibody induce the synergistic inhibition of cyclin D-cdk4 and cyclin E-cdk2 protein kinase activity and induction of p27. Our inference from the work of our colleague A. Koff is that the p27 effect is secondary to the cdk-kinase inhibition. Our current work focuses on the mechanism of cdk inhibition, and investigating whether this synergy occurs in a subset of breast cancers that lack Ras activation.

Geldanamycin - Platinum:

Another interest of our group is the ansamycin antibiotic geldanamycin (GM). This drug is a natural product that binds to a specific pocket in the chaperone protein hsp90 and thereby induces the ubiquitin and proteasome-dependent degradation of certain signalling proteins that require hsp90 for their proper folding or stability. These include steroid receptors, Raf kinase, and transmembrane tyrosine kinases. The most sensitive targets we have identified are the HER-

family protein kinases. We have gone on to show that breast cancers with amplified HER2 are two orders of magnitude more sensitive to GM than are other tumor cell lines. We went on to show that GM inhibition of signal transduction actually leads to inhibition of tumor cell proliferation by a quite specific mechanism - decreased D-cyclin expression and Rb-dependent G_1 arrest. Rb-negative tumors no longer block in G_1, as expected from the mechanism. Instead, they arrest in early anaphase. This anaphase arrest is dependent on the absence of Rb and suggests a role for this protein in the regulation of mitotic transit when the cell is exposed to certain types of environmental stress.

Either type of GM-induced growth arrest is followed by apoptosis. These data have, in part, formed the basis for a phase I clinical trial of a GM derivative, 17-allyl-amino-GM. We will perform this trial in collaboration with investigators at the NCI. We will be especially interested in the effects of the drug on breast cancers that overexpress HER2.

GM is a potent inducer of HER-kinase degradation and as such is potentially a much better inhibitor of HER2 or EGFR than are the antireceptor antibodies in current clinical use. We therefore have begun to investigate whether GM also acts synergistically in combination with cytotoxics. In a first, preliminary experiment, we have shown marked *in vitro* synergy with cis-platinum at doses of GM that, by themselves, do not inhibit cell growth. Current work is aimed at performing the phase I trial, continued investigation of the biochemical mechanism for the GM effect on HER2, and exploration of the potential synergy of GM and chemotherapeutic agents.

Task 3: Determination of clinical response to inhibitors of mitogenic signal transduction, taxanes, and combinations of these agents (P.Rosen, A. Seidman)

A variety of extracellular growth factors stimulate cell growth by binding to and activating growth factor receptors in the HER family. These factors activate signalling by inducing heterodimerization between members of this family which include HER1 (EGFR), HER2, HER3 and HER4. We have found that activation of these pathways leads to increased expression of D-cyclins, among other events. We also have preliminary data that shows that the nature of the response of tumor cells to inhibitors of tyrosine kinases or to FTIs is dependent upon their p53 and Rb status.

Paclitaxel causes arrest of cell cycle progression in the M, or mitotic phase of the cell cycle, with accumulation of cells at the G_2-M interphase. Progression from G_1 to S phase is regulated by phosphorylation of the retinoblastoma gene product, pRb, a transcriptional regulator. Cyclin D1 can mediate phosphorylation and thus functional inactivation of pRb. Furthermore, dephosphorylation of pRb occurs in late M phase. A checkpoint blockade at the G_1/S boundary would be expected to lead to paclitaxel-induced apoptotic cell death. Several investigators have shown paclitael's ability to induce apoptosis through a non-p53-dependent pathway, possibly involving molecular regulators of apoptosis such as Bcl-2, Bax (7), Bcl-xs and -xl, and $p27^{kip}$.

We have previously demonstrated that human breast cancers overexpressing HER2 as assessed immunohistochemically by a monoclonal antibody directed at the extracellular domain of HER2 (4D5, the murine homologue of Herceptin™) were significantly more likely to respond to single agent therapy with paclitaxel or docetaxel (8). However, when we performed the same analysis with a polyclonal antibody, pAb-1, this relationship was no longer observed. We are

presently investigating whether is apparent discordance reflects random chance, or is in some manner mechanistically related to HER2 function and signalling. We are presently anayzing tissue specimens utilizing a unique HER2 antibody (PN2A) specific for phosphorylated (e.g. activated) HER2 receptor for correlation with clinical outcome to tyrosine kinase receptor antibody (and ultimately, taxane and taxane + antibody) therapy for metastatic breast cancer, in collaboration with Drs. David Stern and Michael DiGiovanna of Yale University (9). Our preliminary results have motivated a correlative science project designed to further examine these relationships within the Cancer and Leukemia Group B cooperative group.

We have created and continue to actively expand our computer database of 363 patients (target number: 400) who have participated in clinical trials of taxane (paclitaxel or docetaxel) chemotherapy (n=308), and paclitaxel + anti-tyrosine kinase growth factor receptor monoclonal antibody therapy {paclitaxel + C225, a chimeric anti-EGFR antibody, n=12; paclitaxel + trastuzumab (Herceptin^{TM}), n=43}. This database includes patient demographic characteristics: age, extent of metastatic disease, extent of prior therapy, visceral dominant disease/not, performance status, prior anthracycline exposure, performance status, as well as the results of immunohistochemical evaluation of molecular markers: ER, PR, EGFR, HER-2/*neu*, p53, cyclin D1, pRb, $p27^{kip}$, Bcl-2, and Bax. Our database is 72% complete with regard to availability of data and entry of availability of data.

We have had to overcome one important and unexpected obstacle in the pursuit of this task, that is the resignation of Dr. Paul Peter Rosen from Memorial Sloan-Kettering Cancer Center in August 1998. Dr. Barbara Susnick and Dr. Victor Reuter have assumed the responsibility for the Department of Pathology to ensure the proposed work is completed, and Dr. Rosen has provided guidance prior to his departure to ensure as smooth a transition as possible (see Appendix B). Crispinita Arroyo continues in her prior capacity within the Department of Pathology for this project task.

We anticipate that database building and completion will occur in the next several months, and that statistical data analysis can then be performed. We have been fortunate enough to have entered nearly two patients per week on our ongoing phase II trial of weekly paclitaxel + trastuzumab, as available tumor tissue from these 43+ patients will serve as an important resource for our final multivariate analyses.

CONCLUSIONS

The enhancement of chemotherapeutic agents with novel agents that perturb signal transduction pathways may allow for therapy with a higher therapeutic index due to variable effects on malignant and non-malignant cells, likely due to tissue-specific differences in cell cycle checkpoint regulation (10). However, based on our clinical experience to date with the HC Mab C225 directed against EGFR (HER1) and paclitaxel combinations, we find it highly unlikely that it will be possible to uncouple the synergistic effect observed in skin from the potential synergy expected in breast cancer. Hence, as reported, we have made significant progress in evaluating the combination of weekly paclitaxel + trastuzumab (Herceptin^{TM}).

We have previously demonstrated the clinical activity of the humanized monoclonal antibody directed against the related tyrosine kinase growth factor receptor, HER2/*neu* (rhuMab HER2)(11). A large, multicenter randomized clinical trial reported upon at the 1998 annual meeting of the American Society of Clinical Oncology indeed demonstrated important *clinical synergy* for the combination of paclitaxel and rhuMab HER2 (trastuzumab) (4). Given this successful demonstration of preclinical synergy, and the obstacles we have encountered in combining paclitaxel with HC Mab 225 (*vide supra*) we have refocused our laboratory investigations in an effort to define the mechanisms of this apparent synergy, and to examine the potential synergy of other agents that act downstream in the signal transduction cascade, such as farnesyl transferase inhibitors. Furthermore, we have extended our correlative science investigation to better characterize the molecular correlates of treatment response to taxanes, inhibitors of mitogenic signal transduction, and combinations of these agents (e.g. paclitaxel + trastuzumab, paclitaxel + FTI). Already this work has translated into phase I/II trials, as well as impending phase III evaluation within the Cancer and Leukemia Group B.

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APPENDIX A

1999 ASCO OFFICIAL ABSTRACT FORM

ONLY OFFICIAL 1999 ABSTRACT FORMS WILL BE ACCEPTED. DEADLINE FOR RECEIPT OF PAPER SUBMISSION ABSTRACTS IS DECEMBER 3, 1998. THE ELECTRONIC SUBMISSION PROGRAM GENERATES AN ELECTRONIC OFFICIAL ABSTRACT FORM.

Type abstract below using a 10-point typeface. It is recommended to limit abstract text to 300 words excluding abstract title, authors' names and affiliations.

WEEKLY (W) HERCEPTIN (H) + 1 HOUR TAXOL (T) : PHASE II STUDY IN HER2 OVEREXPRESSING (H2+) AND NON-OVEREXPRESSING (H2-) METASTATIC BREAST CANCER (MBC). M Fornier, AD Seidman, FJ Esteva, M Theodoulou, M Moynahan, V Currie, M Moasser, N Sklarin, T Gilewski, A Surbone, C Denton, D Bacotti, J Willey, A Bach, V Reuter, G Hortobagyi, L Norton, C Hudis. Memorial Sloan-Kettering Cancer Center, NY, NY, M.D. Anderson Cancer Center, Houston, TX.

Successful translation of preclinical synergy (Baselga et al. Cancer Res 58:2825-2831, 1998) to clinical benefit (Slamon et al. Proc ASCO '98) has been demonstrated for T (q 3 W) + H (W). Dose-dense W 1hr T is active and well tolerated (Seidman et al. J Clin Oncol 16:3353-3361, 1998). We treated 42 pts with MBC with W 1hr T + H. After dexamethasone 10 mg., diphenhydramine 50 mg., and cimetidine 300 mg, T 90 mg/m^2 is given over 1hr., followed by H 2 mg/kg. over 30 min., all i.v. (H loading dose 4 mg/kg over 90 min., week 1). Median (M) age: 50 yrs (33-67), M Karnofsky Performance Status 90% (70-100), M organ systems with MBC: 3(1-5); 86% of pts had visceral dominant disease. Pts had 0 (7%), 1 (71%), 2 (17%), or 3 (5%) prior regimens: 17% prior (>1 yr) taxane, 79% prior anthracycline (A); 21% were A-refractory. 607 infusions have been given, M 16/pt (1-25). M delivered dose intensity to date is 82 mg/m^2/wk (57-90). Peripheral neuropathy is the major dose-limiting toxicity (grade 2:35%, grade 3:8%); grade ¾ neutropenia: 10% of pts, with 2 episodes of febrile neutropenia (0.3% of infusions). Other grade ¾ toxicity: diarrhea (7%), onycholysis with infection (7%). Serial ventriculography shows no significant decline in LVEF at week 8 (n=35) or 16 (n=25). One cardiac event: a pt completing a cumulative A dose of 615 mg/m^2 4 weeks prior to T+H had transient CHF. 23/36 evaluable pts have responded (64%; 95% CI 42-76%), 3 with CR (skin + nodes, lung, liver). Responses among H2+ pts: 20/28 (71%; 95% CI 52-81%), H2- pts: 3/8 (37.5%; 95% CI 14-66%).W T+H is active and safe in MBC. Accrual continues to better characterize efficacy, particularly for H2- pts. H is integrated into CALGB 9840, comparing W T(1h) + H to q 3W T(3h) + H. Support:Genentech.

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James Ewing Alumni Chair in Pathology

June 23, 1998

Andrew D. Seidman, M.D.
Breast Cancer Medicine Service
H1009

Dear Dr. Seidman:

Thanks for your e-mail message regarding the Department of Defense Breast Cancer Research Program grant. We have made arrangements by which Dr. Barbara Susnik, who is completing her oncologic pathology fellowship and who will be the Breast Pathology fellow beginning July 1, 1998, will be reviewing all of the immunohistochemical stains carried out in the Breast Pathology Laboratory. I have already discussed this matter with Dr. Rosen, who indicated to me that he would be instructing Dr. Suskik on the logistics of the operation. She has manifested her willingness and interest to perform this task, and I think it will be quite appropriate to regard her as a collaborator in this effort, also for the purposes of potential publications. Dr. Victor Reuter, who is the Head of the Immunohistochemistry Laboratory, has kindly agreed to act as a consultant for the immunohistochemical component of the project, if need arises.

Sincerely,

Juan Rosai, M.D.

db

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